REMARKS

Claims 13-20 have been canceled as drawn to a non-elected invention. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications. Claims 7-12 have been retained as methods of use of the compositions of matter of claims 1 and 3 that depend from and are of the same scope as claims 1 and 3 and are therefore subject to rejoinder pending allowance of claims 1 and 3 in accordance with *In re Ochiai* and the MPEP § 821.04.

The Examiner stated that the following are the remaining rejections.

35 U.S.C. § 101, Rejection of Claims 1-6

The Examiner has maintained the rejection of claims 1-6 under 35 U.S.C. § 101, pertaining to the lack of a specific and substantial utility or a well established utility for the reasons of record in paper No. 10. The Examiner reviewed applicants arguments and evidence regarding applicants assertions that human tumor cell lines, in particular the BT20 human breast cancer cell line, are generally acceptable models for human cancers for identifying genes specifically expressed, or differential expressed, in human cancers. The Examiner, however, reiterated her allegations that "there is widespread belief in the scientific community that they (human tumor cell lines) are not representative of the tumors from which they were derived..." and citing the previous articles of record submitted with the previous Office Action. The Examiner also reiterated her argument that the breast cell line, BT20, used in the claimed invention "seems not to be from the same subset of primary breast carcinoma taught by Wistuba et al."

Applicants Response

Applicants reiterate their position that the Examiner has not established by a "preponderance of evidence" that there is "widespread belief ... that human tumor cell lines are not representative of the tumors from which they were derived...", in particular, that the BT20 human breast tumor cell line used in the claimed invention, is not useful for that purpose. Applicants have provided several published articles attesting to the fact that the BT20 cell line is commonly used as a model system for determining gene expression patterns in breast cancer. See the Lee article, No. 11 of the IDS, and the Mitchell, Williamson, and Chen articles, Exhibits A-C of the previous response, filed 4/02/2003. The fact that the Witsuba article, cited by applicants in the

specification, does not specifically recite this cell line does not provide evidence one way or the other as to its usefulness in modeling human breast cancer. The Witsuba article was cited in the background of the invention as an example of the established usefulness of human mammary epithelial cells at various stages of breast cancer in studying malignant transformation and tumor progression of the disease.

Further, the Examiner now alleges that because the data of Table 1 is the result of Northern analysis, the findings do not confer utility on SEQ ID NO:2. This is because, the Examiner stated, it is known in the art that the cDNA libraries used for the electronic Northerns are made up of a "representative" population of clones. However, the Examiner noted, that cells in the human body encode approximately 100,000 genes (emphasis added) of which 10,000 and 20,000 are thought to be expressed as mRNA. It is clear, the Examiner stated, that not all of the genes expressed as mRNA are represented in the libraries of the claimed invention. Thus, the fact that the claimed polynucleotide is not expressed in one or another library appears to be an artifact of the analytical system and cannot be extrapolated to a prediction of whether that molecule is expressed in the tissue "represented" by the library.

Applicants Response

Applicants first of all point out that the data in Table 1 does not represent electronic Northern analysis, rather the data represents actual wet lab experiments conducted in a microarray format as described at p. 5, line 30 through p. 6, line 3 of the specification, and using the techniques specifically described in Example VII at pp. 33-35 for Polymer Coated Slide-Hybridization.

In addition, however, applicants challenge the Examiners' latest allegation regarding the sufficiency of Incyte's database in adequately representing the number of cDNAs expressed in tissue libraries. The Examiner's only apparent "evidence" in support of this allegation is a statement that "cells in the human body encode approximately 100,000 genes of which between 10,000 and 20,000 are thought to be expressed as mRNA". Thus, the Examiner stated, it is clear that not all of the genes expressed as mRNA are represented in the libraries of the claimed invention. Applicants first of all challenge the accuracy of the Examiner "facts" regarding the number of genes in the human body and the number of expressed genes in any given tissue. The

MPEP at § 2144.03 and the CFR § 1.104 (d)(2) state that where the Examiner relies on common knowledge in the art:

> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner. Such an affidavit is subject to contradiction or explanation by the affidavits of the applicant and other persons.

It is further noted in the communication from the USPTO issued by Stephen G. Kunin, Deputy Commissioner for Patent Policy on February 21, 2002 and entitled Procedures for Relying on Facts Which are Not of Record as Common Knowledge or for Taking Official Notice, that:

> It would not be appropriate for the Examiner to take official notice of facts without citing a prior art reference where the facts to be well known are not capable of instant and unquestionable demonstration as being well-known (original emphasis).

The Examiner has not presented any evidence in support of her allegation that the Incyte database is under representative of actual gene expression. In particular, applicants challenge the Examiners' statement that "cells in the human body encode approximately 100,000 genes of which between 10,000 and 20,000 are thought to be expressed as mRNA". Applicants reference the enclosed article entitled "So, how many genes are there?" recently released from the U.S. Department of Energy, Office of Science clearly showing that the actual number of genes in the human genome is still in doubt and that estimates range from 27,000 to 150,000, with the most recent estimates predicting around 30,000 genes. Applicants further attest to the following (and which can be made by expert declaration if the Examiner so wishes): It is well known in the art that only about 10% of the genes are expressed in a cell or tissue at any one time (Soares et al. (1994) Proc Natl Acad Sci USA, 91:9228-9232), and this difference is ultimately how cells and tissues differ from one another. After empirical studies were completed in 1996, it was determined that the libraries in the Incyte database would be sequenced to a level appropriate for estimation of gene expression in that cell or tissue. Further, between 1992 and 1999 (when this case was first filed), the methods used to construct (and sequence) the libraries improved rapidly along with technology development, i.e., cloning cDNA inserts, changed from only using oligo-

d(T) priming to include subtraction (first developed in the late 1980's), normalization (first developed in the early 1990's), and 5' priming of the clone insert (which increases the likelihood of finding and completing full length reading frames). Each of these techniques helped to maximize full representation of expressed sequences in the database.

Applicants would aver that the overwhelming majority of genes are well represented and that their expression can be properly estimated using the Incyte databases and software. In fact, this is especially true for those libraries which represent matched diseased and cytologically normal samples from the same donor (as in the instant case, see Table 2) and when expression in all libraries with a particular disease, e.g., a cancer, are compared with expression in all similar tissue libraries with cytologically normal tissues. Also from the paragraphs above, the Examiner must concede that sequencing to levels of about 3,000 to about 10,000 cDNAs, as utilized in the Incyte databases is representative of about 10% expression as it is known in the art. Thus the Examiner provides no factual evidence in support of her allegation that "it is known in the art that the cDNA libraries used for the electronic Northerns are made up of a "representative" population of clones" and therefore that Incyte's database of cDNAs underrepresent the actual numbers of mRNAs expressed in any given tissue at any given time.

The exhibits presented above in support of applicants arguments regarding the sufficiency of the Incyte cDNA library database are timely presented considering that the Examiners' allegation has been made for the first time in the Final Office Action, and therefore provides good and sufficient why the evidence was not presented earlier and should now be considered.

Moreover, the Office Action has ignored the fact that the recited polynucleotides and encoded polypeptides have specific, substantial, and credible utilities in, for example, toxicology testing in drug discovery, in particular, drug discovery related to the treatment of breast cancer. One of skill in the art would know that, as a part of such toxicology testing, the recited polynucleotides could be used to detect toxic side effects of drug candidates targeted to a particular polypeptide in terms of their effects on the expression of other genes and their encoded polypeptides using any of a number of methods well known in the art for studying differential gene expression, in particular, in a microarray format. See, in particular, the specification, at p. 6, lines 21-25, and at p. 14, lines 4-11. Therefore, the claimed polynucleotides meet the utility requirement of 35 U.S.C. § 101 based at least on the well-known, specific, and substantial

utilities of expressed, naturally occurring polynucleotides in toxicology testing and drug discovery.

In support of this well-established utility for the claimed invention, Appellants submit with this response the Declaration of Dr. Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on April 23, 2001] that cDNA microarrays that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating breast cancer for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

This Declaration and associated exhibits is being presented prior to the filing of any appeal on the case and is therefore timely presented in accordance with 37 CFR 1.195.

I. The use of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Chen '746 application on April 23, 2001 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed

at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that the "Chen '746 specification would have led a person skilled in the art on April 23, 2001 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of breast cancer [a] to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on April 23, 2001] that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating breast cancer for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-April 23, 2001 publications showing the state of the art on April 23, 2001 (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts [(a)-(f)], he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development in October 2000 (and for several years prior to October 2000) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Chen '746 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Chen '746 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Chen '746 application at the time it was filed "would have wanted their cDNA microarray to have a SEQ ID NO:1-encoding polynucleotide probe because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to April 23, 2001" (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Chen '746 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on p. 14 of the Chen '746 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-April 2001 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Chen '746 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application

filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Chen '746 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999).

In another pre-April 2001 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This

discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

C. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1-6

The Examiner has also maintained the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph pertaining to lack of support by a specific and/or substantial utility for the reasons of record.

To the extent that this rejection is based on an improper grounds of rejection of the claimed invention for lack of a well established or specific and substantial asserted utility for the reasons give above, this rejection should be withdrawn for the same reasons.

35 U.S.C. § 112, First Paragraph, Written Description, Rejection of Claims 1(b) 2(b) and 3-6

The Examiner has maintained the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph for lacking a clear description of a polynucleotide encoding a naturally occurring amino acid sequence having at least 95% sequence identity to SEQ ID NO:1, or a naturally occurring polynucleotide having at least 95% (sic, 90%) sequence identity to SEQ ID NO:21 (sic, 2) for the reasons of record in paper No. 10.

The Examiner reviewed applicants response to this rejection, specifically as presented at pp. 10-14 of the response filed 4/02/2003. The Examiner stated that applicants arguments have been considered but are not deemed persuasive, and reiterating essentially the same arguments previously presented in paper No. 10, at pages 12-17.

Applicants Response

Applicants reiterate the arguments previously presented and reviewed by the Examiner, specifically at pp. 1-14 of the response filed 4/02/2003, in particular, that the subject matter of the claims, in particular claims 1(b) and 2(b) are defined in terms of the chemical and structural features of SEQ ID NOs:1 and 2 and, accordingly, the specification provides an adequate written description of the claimed variant sequences. Withdrawal of the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph is therefore requested.

35 U.S.C. § 112, First Paragraph, Scope, Rejection of Claims 1 and 3-6

1. The Examiner has maintained the rejection of claims 1 and 3-6 under 35 U.S.C. § 112, first paragraph, pertaining to the lack of enablement for a polynucleotide "encoding " the polypeptide of SEQ ID NO:1, and a method of making said polypeptide, for the reasons of record in paper No. 10.

The Examiner reviewed applicants response to this rejection, specifically as presented at pp. 15-16 of the response filed 4/02/2003. The Examiner stated that applicants arguments have been considered but are not deemed persuasive for essentially the same reasons given in paper No. 10, in particular at 19-20. In response to the Lewin article, cited by applicants, the Examiner stated that the Lewin reference does not support applicants statement that "mRNA levels are usually a good indicator of protein levels in a cell" because the Lewin reference does not disclose a correlation between mRNA and protein levels of expression (emphasis added). The Examiner stated further that the recited references by the Examiner are only some of the examples of negative translational regulation, and that it is well known in the art that both translational and post-transcriptional control are an important step in the control of gene expression (emphasis added).

Applicants Response

Applicants reiterate the arguments and exhibits presented previously in response to this rejection and, in particular, that the Lewin article does support applicants statement that mRNA levels are usually a good indicator of protein levels in a cell. Specifically, the Lewin article states that "For most genes, this (transcription) is a major control point; probably it is the most common level of regulation (emphasis added), and further states "the overwhelming majority of regulatory events occur at the initiation of transcription" (emphasis added). Clearly, these statements support applicants position that it is generally accepted in the art that for most genes mRNA

transcription is usually a good indicator of levels of protein expression as well. Applicants point out that the Lewin article is excerpted from a textbook on genes and gene regulation, and as such is representative of what is "well known" in the art. The fact that the article does not disclose experimental data correlating mRNA and protein levels does not detract from the factual basis for the statements made, and therefore supports applicants contention that the Examiners' evidence for the "potential" for post-transcriptional regulation of SEQ ID NO:1 expression does not provide specific evidence that one skilled in the art would doubt the substantial likelihood that the expression of SEQ ID NO:1 is, like most genes, controlled at the transcriptional level and therefore likely correlated with levels of SEQ ID NO:2 mRNA expression.

2. The Examiner has also maintained the rejection of claims 1(b), 2(b), and 3-6 under 35 U.S.C. § 112, first paragraph, for lacking enablement for a polynucleotide encoding a naturally occurring amino acid sequence having at least 95% sequence identity to SEQ ID NO:1, or a naturally occurring polynucleotide having at least 95% (sic, 90%) sequence identity to SEQ ID NO:2, for the reasons of record in paper No. 10.

The Examiner reviewed applicants arguments presented in the response filed 4/02/2003 at pages 17-18, and stated that applicants arguments have been considered but are not deemed persuasive for the following reasons. Applicant has not taught how to use the invention for the reasons previously set forth for utility. Further, the Examiner stated, no consensus sequences that identify the claimed polynucleotide variants are disclosed, *supra,* and thus one cannot identify the claimed variants.

Applicants Response

Applicants first of all reference all arguments previously and presently made with respect to both well established and specific and substantial asserted utilities for the claimed invention, and therefore that one of skill in the art would clearly know how to use the claimed invention. Secondly, with regard to the Examiners' remarks regarding the lack of "consensus" sequences for the claimed polynucleotide variants, applicants reference the remarks made in the previous Response to Office Action filed 4/02/2003, in particular at the last paragraph of p. 17. Applicants reiterate that the described uses of the polynucleotides of the invention, including variant sequences, does not require a functional association for the encoded polypeptide.

For all of the above reasons, applicants submit that the claimed polynucleotides, as recited in claims 1 and 3-6 are fully enabled by the specification, and therefore request withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited. Applicants further request that, upon allowance of claims 1 and 3, that claims 7-12 be rejoined and examined as methods of use of the compositions of matter of claims 1 and 3 that depend from and are of the same scope as claims 1 and 3 and are therefore subject to rejoinder pending allowance of claims 1 and 3 in accordance with *In re Ochiai* and the MPEP § 821.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: August 4, 2003

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